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Non-invasive MR-guided HIFU Therapy of TSC-Associated Renal Angiomyolipomas

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14. ABSTRACT
This report is a summary of our first year's work on the proposed research. During this period, our effort was focused on technological development for thermal ablation in mice. Our goal was to establish a small-animal MR-guided HIFU experimental system that enables simultaneous HIFU ablation and MR guidance. This goal was achieved and our experimental results demonstrated the b asic function of t he experimental system in in-vitro stu dies. We have laid the groundwork for t he feasibility investigation of mouse tumor ablati on in the second year. Based o n the current progress, we will continue work o n our technological improvement of MR-guided HIFU system for in-vivo studies. We believe this system will be ready for animal experiments after several further in-vitro studies in two or three months.

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MR-guided HIFU, renal angiomyolipoma, tumor, ablation, thermal therapy, TSC

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Introduction

The overarching goal of our research is to develop a non-invasive technique for clinical management of TSC-associated renal angiomyolipomas. TSC is a genetic tumor predisposition syndrome characterized by the growth of lesions in multiple organ systems. Approximately 80% of TSC patients develop renal angiomyolipomas, a type of lesion composed of variable amounts of fat, smooth muscle, and vascular tissue. Renal angiomyolipomas are often benign and present with multiple lesions in each kidney. Patients with renal angiomyolipomas may experience discomfort, flank pain, hydronephrosis, hematuria, and hypertension. These lesions can also lead to acute hemorrhaging or chronic loss of renal function.

The technique we are developing uses High Intensity Focused Ultra sound (HIFU) to ablate tumors and magnetic resonance (MR) imaging to monitor ablation. MR-guided HIFU enables "surgical procedures" to be performed deep within the body without incisions or punctures, providing a risk-free therapeutic approach to managing renal angiomyolipomas. The physical mechanisms underlying HIFU is that a HIFU transducer constructed with a concave shape and/or multiple elements has the ability to focus acoustic energy into a target volume having a diameter of a few millimeters. The focused acoustic energy induces a rapid rise in temperature (e.g. 70°C to 100°C), resulting in thermal necrosis of tissues in the target volume. Although HIFU offers the capability of thermal ablation, non-invasive thermal therapy is possible only if the focal spot of HIFU can be controlled within the body using the feedback information provided by medical imaging guidance. MR is superior to other imaging modalities because it provides both excellent soft-tissue visualization and the ability to monitor thermal delivery (temperature mapping).

The proposed research is a two-year pre-clinical study that aims to investigate whether MR-guided HIFU offers the ability to ablate renal angiomyolipomas in a mouse tumor model. From this animal study, we expect to gain research experience that will benefit future clinical study on non-invasive thermal therapy of renal angiomyolipomas in human subjects. The obtained experimental results will be used to apply for grant funding that will support our further work on MR-guided HIFU. In the proposed work, we had planned our first year on the development of an MR-guided HIFU experimental system for thermal ablation in mouse kidneys. The technical challenge we expected to meet was the respiratory movement of kidneys in mouse ablation. We proposed to use parallel MR imaging technology to track the respiration in order to enable real-time MR guidance for HIFU ablation in mouse.

This report is a summary of our first year's work on the proposed research. During this period, our effort was focused on technological development for thermal ablation in mice. Our goal was to establish a small-animal MR-guided HIFU system and enable efficient thermal delivery deep within the mouse body. The following list highlights the primary progresses we have made:

1. An animal HIFU system was purchased and installed on our research Philips 3T MR scanner at the Cincinnati Children's Hospital Medical Center (CCHMC) Imaging Research Center (IRC).
2. A feedback control MR-guided experimental system was established using the Philips 3T MR scanner and the installed animal HIFU system.
3. MR temperature mapping using MR phase signals was demonstrated in in-vitro studies (phantom and pig liver).
4. We found that respiratory movement in mice does not affect thermal therapy as significantly as expected. Instead, the primary challenge in our work arises from the interface between transducer and mouse body. This finding changed our technological focus in research development.
5. We constructed a mechanic stage that can provide a water interface for ultrasound wave propagation. This will be used to tackle the new technical issues we found in our work.
6. The whole MR-guided HIFU experimental system was demonstrated functional. Based on this ground work, we will proceed animal studies in the second year.

Our first year's work laid the groundwork for the feasibility investigation of mouse tumor ablation we planned for the second year. Based on the current progress, we will continue work on our technological solution to mouse thermal ablation and improve the performance of MR-guided HIFU system. We believe this system will be ready for animal experiments in two or three months after several in-vitro studies. We expect to start animal ablation in the first half of the second year of this research.

Body

Proposed Task 1: Design and development of an MR-guided HIFU experimental system for thermal ablation in a phantom study (Stage 1: Months 1-12).
An MR-guided HIFU experimental system will be designed for thermal ablation. The MR coil hardware will be constructed and integrated with a HIFU system for small animal research in a Philips 3.0 T multi-channel whole body MR imaging system. The software components will be developed for MR guidance and HIFU control. The basic function of the entire system will be tested using a phantom.

Research accomplishment: A small-animal HIFU system (Philips HealthCare, Vantaa, Finland) was purchased and installed on the IRC Philips 3.0 Tesla MRI scanner at the Cincinnati Children's Hospital Medical Center. This system includes an eight-channel 3.0 MHz sectored ultrasound transducer, a high-efficiency generator for acoustic power control, and a stand-alone console that can be used to control the HIFU power transmission and communicate with the MRI scanner. Figure 1 shows the experimental setup scheme and pictures for thermal ablation in phantoms and animals. This setup allows the HIFU console to synchronize MRI scanning when running HIFU thermal ablation. The acoustic power delivery from the HIFU transducer can be dynamically updated by the HIFU console based on MRI information. This provides a feedback control for the thermal delivery deep within the body.

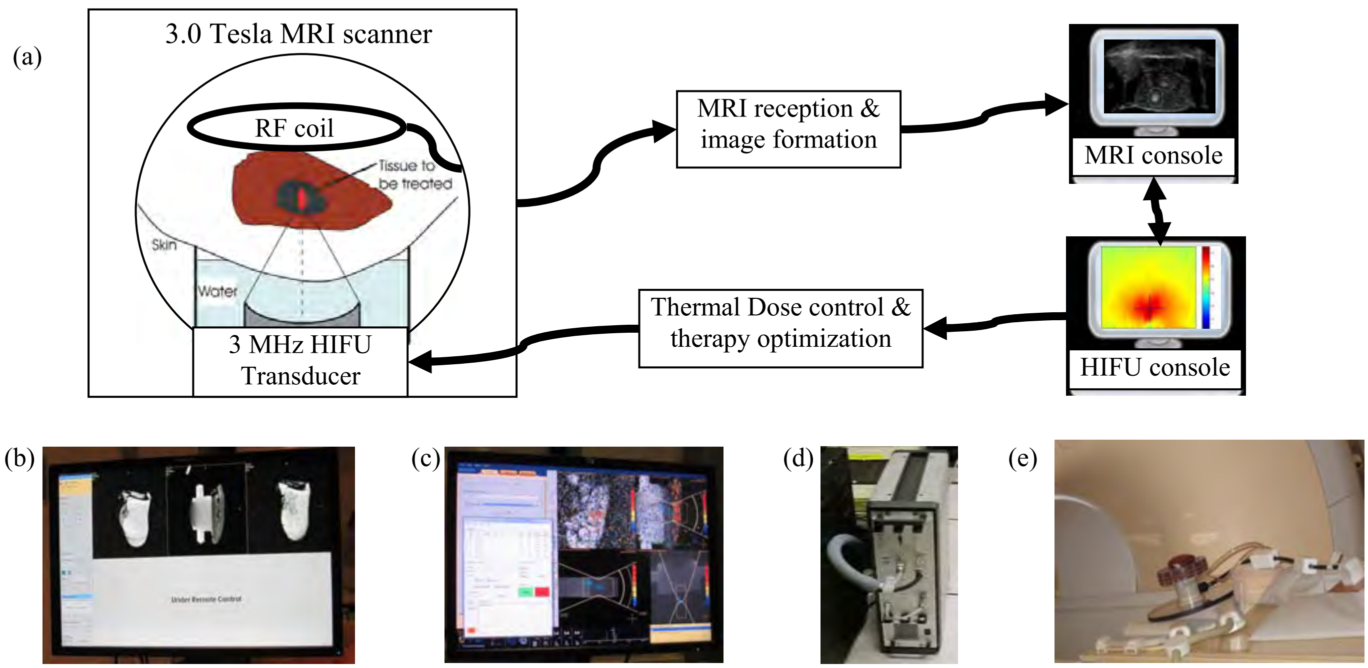

Figure 1. *A feedback control system for preclinical thermal therapy was established using MR-guided HIFU in the CCHMC IRC. The feedback control loop is formed using a 3.0 Tesla 32-channel Philips Achieva MR scanner (Philips HealthCare, Best, the Netherlands) and a Philips small-animal HIFU system (Philips HealthCare, Vantaa, Finland). This system uses an eight-channel 3 MHz sectored transducer (IMASONIC, Voray sur l'Ognon, France) for acoustic transmission. (a) Experimental setup scheme. (b) MRI console. (c) HIFU console). (d) High-efficiency generator for HIFU transducer. (e) Transducer, cables and phantoms inside the MRI scanner.*

<u>New challenges were found in our preliminary studies</u>: Using a few preliminary experiments with the established MR-guided HIFU experimental system, we found a new challenge in small-animal HIFU ablation. As shown in Figure 2, a HIFU ablation experiment was conducted using a homogeneous phantom. A HIFU lesion of ~ 2 millimeter was successfully developed within the target region. The MR phase signals showed dynamic variation associated with temperature rise within the HIFU lesion, indicating the temperature can be effectively monitored during the ablation. However, in our first attempted in-vivo study (mouse ablation), we found the HIFU lesion cannot be formed although we kept the mouse static using sedation during the HIFU ablation. As shown in Figure 3, the temperature mapping indicated that a focal spot could not be produced within the static target region in the mouse. After further investigation, we found that the problem arises from

the interface between transducer and the animal body. Since the animal body is small with respect to the focal length of the transducer (5 centimeter), we have to put water between the transducer and the animal body as acoustic interface. However, the small air bubbles in the water introduce phase incoherence of the acoustic waves transmitted from different channels of the HIFU transducer. As a result, the acoustic energy cannot be focused within the target region due to phase cancellation of acoustic waves.

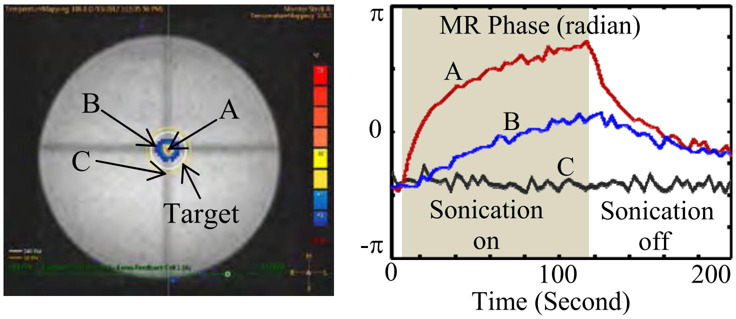

Figure 2. HIFU thermal ablation and temperature mapping in a homogeneous phantom. A HIFU lesion of ~ 2 mm can be formed using feedback control in Figure 1. The plots show MR phase signals change with temperature and provide an approach to tracking and optimizing HIFU thermal delivery. The color maps overlaid on the MR image gives the temperature mapping in HIFU ablation.

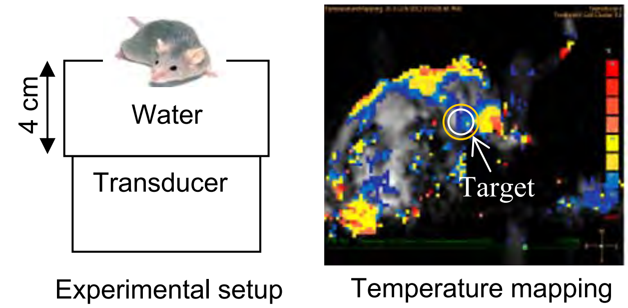

Figure 3. First attempted mouse HIFU ablation. Because there are air bubbles in the ware interface between the transducer and the animal body, a HIFU lesion cannot be effectively formed. The temperature mapping shows the acoustic energy is spread over the whole body.

Proposed Task 1a: Hardware development (Months 1-4).
A radiofrequency (RF) coil will be designed and developed for abdominal imaging in mice. The number of receive channels will be determined experimentally for optimum SNR and imaging acceleration performance in mouse imaging. This coil will be integrated with a HIFU system for small animal research on a Philips 3.0 Tesla multi-channel MR imaging system.

Research accomplishment: A small-animal MRI coil was constructed (Figure 4a). This coil provided better SNR for mouse imaging than other coils on the IRC Philips 3T MRI scanner. The SNR gain factor was estimated to be ~ 3 over the commercial small-animal coil provided by Philips HealthCare. A mechanic stage (Figure 4b) was built for holding/stabilizing the animal/phantom and the coil in HIFU experiments within the MRI scanner. This stage has an empty space inside and is sealed outside. The sealed space is used to accommodate water for interfacing acoustic pathway between the transducer and the target. There are two tubes (Figure 4b) connected to the internal space inside the stage. These tubes are used to fill the water into the stage and remove the air bubbles in the water. This design will be used to address the interface problem we found in our first attempted in-vivo experiments. We expect to try in-vivo experiments using this new design in the coming two or three months.

Figure 4. An MRI coil (a) was built for mouse imaging on Philips 3T scanner. A mechanic stage (b) was constructed for holding/stabilizing the mouse and the coil within the MRI scanner. Inside the stage, water will be used as the interface between the HIFU transducer and the animal.

All the hardware has been tested on the MRI scanner. The test demonstrated that the hardware is MR compatible. In addition, we experimentally compared our MR imaging results with those using commercial hardware. The experiments showed that our hardware offers better MR imaging quality than commercial hardware provided by Philips HealthCare. The new hardware we developed has been integrated with MR scanner system and ready for MR-guided HIFU experiments in the in-vitro and in-vivo studies.

Proposed Task 1b: Software development (Months 5-10).
Dynamic parallel imaging and motion correction methods will be developed on Philips 3.0 Tesla multi-channel MR imaging system. Real-time reconstruction will be implemented. Four major imaging methods, T_1 weighted imaging, T_2 weighted imaging, stiffness weighted imaging, and phase imaging, will be developed using parallel

imaging. Data processing methods will be developed to extract multi-source information, including lesion position, temperature, acoustic force under HIFU, and tissue destruction in therapy, from real-time MR images. A control algorithm will be developed to dynamically optimize the localization and power of HIFU focal spot based on real-time and multi-source feedback information.

Research accomplishment: The software development work has been accomplished in collaboration with Philips HealthCare during the last several months. This collaboration includes the setting up of the imaging protocols for animal HIFU ablation, the configuration of software for feedback control of HIFU transducer, and the verification of MR guidance for HIFU ablation. Currently, we have a software package installed on the HIFU console. This package includes a standard Philips clinical software, Sonalleve (*Philips HealthCare, Vantaa, Finland*), and a small-animal HIFU software. The prior one provides the capability of communication with MRI console and processing MRI data. The latter one provides the capability of communicating with the HIFU generator and extracting information from Sonalleve. This package provides a feedback control algorithm for HIFU ablation. A standard Philips MRI protocol was installed on Philips 3T MRI scanner. These protocols provide the capability of imaging animals with different strategies during HIFU ablation and monitoring the thermal delivery in real time. An echo-planar imaging protocol has been developed in combination with our new MR coil and used in MR guidance for HIFU ablation. The temporal resolution for this sequence can reach 1 second. This imaging speed was found sufficient for real-time guidance even when motion exists. We are working on the integration of echo-planar imaging with T1-weighted, T2-weighted, stiffness weighted, and phase imaging methods.

Proposed Task 1c: Test of basic function (Months 11-12).
A phantom model will be designed and developed to simulate the body of a mouse. MR-guided HIFU experimental system will be tested and optimized in a phantom study. Its ability to ablate a pre-selected target in the phantom will be evaluated.

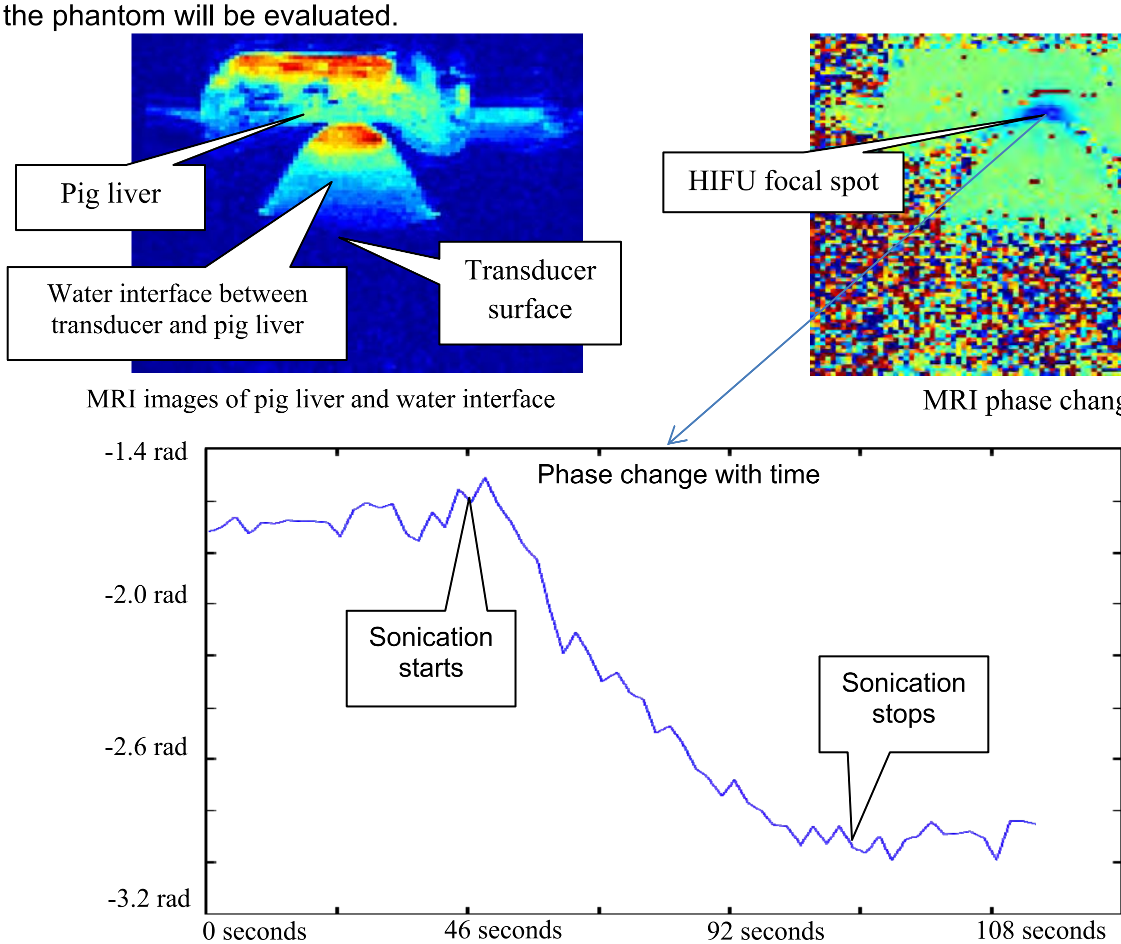

Figure 5. *An in-vitro study (ablation of pig liver) using the established MR-guided HIFU system in Figure 1. The MR phase change mapping shows the acoustic energy is focused within a small local spot of ~ 2 millimeters. The plot shows the phase change with sonication in the center of focal spot. This study demonstrates the basic function of the experimental system we developed in the first year.*

Research accomplishment: We have tested the small-animal MR-guided HIFU experimental system in in-vitro studies. Figure 5 shows an experimental study on MR-guided HIFU using a piece of pig liver. It was found that HIFU offers the capability of deliver ultrasound energy into a small local spot of ~ 2 millimeters. This demonstrates the potential of HIFU to ablate tumors deep within the mouse body. However, in this study on pig liver, we also found that the interface between the transducer surface and the target plays a critical role in HIFU ablation. In the experiment, we used water as interface. The bubbles in the water significantly reduced the efficiency of thermal delivery. We found that HIFU ablation may fail due to the existence of bubbles. We will change the experimental design using the mechanic stage (Figure 4b) developed in the last several months. We expect that this new design can improve the water interface performance and make the in-vivo studies feasible. We expect to start mouse ablation using MR-guided HIFU experimental system in Month 15.

Key Research Accomplishments

1. A small animal MR-guided HIFU experimental system was established at the Cincinnati Children's Hospital Medical Center (CCHMC) Imaging Research Center (IRC).
2. Thermal ablation and MR guidance capability was demonstrated using the established experimental system in in-vitro studies.
3. MR imaging speed using EPI sequence was found sufficient for real-time feedback in HIFU thermal delivery. This addressed the challenge arising from that respiratory movement in mice.
4. We found that the water interface between the transducer surface and the animal body is crucial to the thermal delivery. To address this issue, we constructed a mechanic stage that can provide a water interface for ultrasound wave propagation.
5. All the hardware and software are ready for mouse ablation experiment. We will make a final adjustment of the system in the coming two months before the start of mouse ablation.
6. The small-animal MR-guided HIFU experimental system was demonstrated functional in in-vitro studies. We will proceed our animal studies in the second year.

Reportable Outcomes

1. Based on our preliminary results we obtained in this study, we applied for St. Baldrick foundation research grant. This grant was awarded in July 2012 and provided a support on the purchase of a needle hydrophone system that can measure the acoustic pressure in in-vitro studies. This will provide a direct way to evaluate HIFU transmission in soft tissue and a new technique to monitor HIFU ablation in real time. We are working on how to integrate the new project with the DOD project in order to deliver the best experimental outcomes in a more efficient way.
2. Based on this study, we have developed our collaboration relationship with two research groups at the University of Cincinnati: Dr. Donald French's group [1-2] and Dr. Christy Holland's group [3]. Dr. French is working on inverse imaging problem for HIFU treatment planning and Dr. Holland is working on cavitation mechanisms in cardiac applications of HIFU. We are working on combining these different research projects together for enhancing our ongoing MR-guided HIFU project.

Conclusion

In summary, we have established a small-animal MR-guided HIFU system for mouse ablation and demonstrated the basic function of this new system. The first year of this research has seen the success in technological development. This will lay groundwork for animal studies in the second year of this research. We expect to deliver more promising outcomes by proceeding animal studies in the coming time.

References

1. D.A. French, D.A. Edwards, Perturbation approximation of solutions of a nonlinear inverse problem arising in olfaction experimentation, J. Math. Bio., 2007, *55*(5-6), 745-765.
2. J.M.J. Huttunen, T. Huttunen, M. Malinen, J.P. Kaipio, Determination of herterogeneous thermal parameters using ultrasound induced heating and MR thermal mapping, Phys. Med. Biol., 2006, 51, 1011-1032.

3. K. J. Haworth, T. Do uglas, K. Radhakrish nan, M.T. Burgess, J.A. Kopechek, S. Hua ng, DD. McPherson, C.K. Holland, Passive imaging with pul sed ultrasound insonations, J. Acoust. So c. Am., 2112, 132(1), 544-552.